PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	17 OCT 2005
Applicant's or agent's file reference 265/38	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/IL05/00332	23 March 2005 (23.03.2005)	23 March 2004 (23.03.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 31/7048, 31/353, 35/78 and US Cl.: 514/27; 424/725-779

Applicant

RIMONEST LTD

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [ ] Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	16 September 2005 (16.09.2005)	Amy Lewis Telephone No. (571) 272-2765

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY	International application No. PCT/IL05/00332

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims NONE	YES
	Claims 1-27	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-27	NO
Industrial applicability (IA)	Claims 1-27	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL05/00332

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1, 14, 15 and 27 lack novelty under PCT Article 33(2) as being anticipated by Schmiedel (WO 03/077930, abstract only). The reference teaches a composition containing at least one quercetin flavonoid in combination with at least one saccharide (including short chain fatty acids), thus meeting the component limitations of instant claims 1 and 15.

Claims 1-5, 7, 10, 12, 13, 14, 19, 21, and 23 lack novelty under PCT Article 33(2) as being anticipated by Schubert, SY, et al. ("Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids," 1999 *J Ethnopharmacology* 66: pages 11-17) in view of Boukharta M, et al. ("Biodistribution of ellagic acid and dose-related inhibition of lung tumorgenesis in A/J mice," *Nutr Cancer*. 1992; 18(2):181-9 [abstract only]).

Schubert et al. teach that pomegranate contains flavonoids (a type of polyphenol) and punicic acid. The reference also teaches medicinal flavonoid preparations from the fruit for various conditions. The reference teaches that flavonoids exhibit various pharmacological activities, including anti-inflammatory activity and antioxidant activity, and anti-cancer (protective as well as therapeutic) activity, as well as for the reduction of coronary artery disease. (See abstract and p. 11-12). Thus meeting the limitation of a composition containing a conjugated fatty acid and a polyphenol.

The secondary reference teaches that ellagic acid (EA) is derived from fruit ellagitannins, thus illustrating that EA is an ellagitannin (of instant claims 12 and 13).

Claims 1-17, and 20-23 lack an inventive step under PCT Article 33(3) as being obvious over Schubert SY, et al. ("Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids," 1999 *J Ethnopharmacology* 66: pages 11-17), in view of Harborne & Williams ("Advances in flavonoid research since 1992," *Phytochemistry* 55(6) Nov 2000: p. 481-504).

Schubert is applied as above, teaching the instantly claimed composition of a conjugated fatty acid (punicic acid) and a polyphenol.

Harborne teaches the therapeutic activity of flavonoids as having anti-inflammatory, anti-oxidant, and cytotoxic anti-tumor activity (p. 494-498, section 6.6.1). The reference also teaches flavonoids, including quercetin and caffeic acid, for reducing the risk of coronary heart disease (see p. 492, section 6.3). Thus, Harborne & Williams teach the compositions comprising various flavanoids, as claimed in the instant invention.

It would have been obvious to one of ordinary skill in the art to modify the flavonoid medicinal preparation of Schubert for the treatment a cell proliferative disorder, e.g. cancer, (of instant claims 22 and 23) or atherosclerosis (of instant claims 20 and 21), having been taught by the prior art (Harborne) that the flavonoids quercetin and caffeic acid are useful in treating those disorders. In reference to claims 16 and 17, regarding an oral dosage form, it would have been obvious to one of ordinary skill in the art to make an

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

oral dosage form of the medicine, motivated by ease of administration.

Claims 22-24 lack an inventive step under PCT Article 33(3) as being obvious over Schubert SY, et al. ("Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids," 1999 *J Ethnopharmacology* 66: pages 11-17), in view of Nair HK, et al., "Inhibition of prostate cancel cell colony formation by the flavonoid quercetin correlates with modulation of specific regulatory genes," *Clin Diagn Lab Immunol* 2004 Jan; 11(1):63-9.

Schubert is applied as above, teaching the instantly claimed composition of a conjugated fatty acid (punicic acid) and a polyphenol.

Nair teach that quercetin inhibits the growth of prostate cancer cells.

It would have been obvious to one of ordinary skill in the art to modify the flavonoid medicinal preparation of Schubert for the treatment a cell proliferative disorder, e.g. cancer, (of instant claims 22 and 23), and more specifically for the treatment of prostate cancer (of instant claim 24), having been taught by the prior art (i.e. Nair) that quercitin inhibits the growth of prostate cancer cells, motivated by the desire to make a composition effective to treat prostate cancer.

Claims 16-19 lack an inventive step under PCT Article 33(3) as being obvious over Schubert SY, et al. ("Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids," 1999 *J Ethnopharmacology* 66: pages 11-17), in view of Al-Awwadi N, et al. ("Antidiabetic activity of red wime polyphenolic extract, ethanol, or both in Streptozotocin-treated rats," 27 Jan 2004 *J Agric Chem* 52(4):1008-16), and further in view of Harborne & Williams (*Phytochemistry* 55(6) Nov 2000: p. 481-504).

Schubert is applied as above, teaching the instantly claimed composition of a conjugated fatty acid (punicic acid) and a polyphenol.

Al-Awwadi teaches that polyphenolic extract from red wine (used at the pharmacological dose of 200 mg/kg) for the treatment of diabetic rats.

Harborne teaches the therapeutic activity of flavonoids as having anti-inflammatory, anti-oxidant, and cytotoxic anti-tumor activity (p. 494-498, section 6.6.1). The reference also teaches flavonoids, including quercetin and caffeic acid (see p. 492, section 6.3). Thus, Harborne & Williams teach the compositions comprising various flavanoids, as claimed in the instant invention. In addition, the secondary reference teaches that phenolic constituents of red wine include quercitin and caffeic acid (p. 492, col. 2).

It would have been obvious to one of ordinary skill in the art to use the flavonoid medicinal preparation of Schubert for the treatment of diabetes, having been taught by the prior art that red wine extract is useful in the treatment of diabetes (as taught by Al-Awwadi), and that red wine polypheolic extract contains the flavonoids quercetin and caffeic acid (as taught by Harborne), motivated by the desire to make a composition effective to treat diabetes.

Claims 25 and 26 lack an inventive step under PCT Article 33(3) as being obvious over Schubert SY, et al. ("Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids," 1999 *J Ethnopharmacology* 66: pages 11-17), in view of Han L, et al., ("Anti-obesity action of *Salix matsudana* leaves," *Phytother Res* 2003 Dec;17(10):1195-8).

Schubert is applied as above, teaching the instantly claimed composition of a conjugated fatty acid (punicic acid) and a polyphenol.

Han teaches that flavonoids from polyphenol extracts are effective anti-obesity agents. The secondary reference teaches that mice fed with the extract had significantly reduced adipose tissue weight (abstract).

Having been taught by Han that flavonoids from polypehnol extracts are effective anti-obesity agents, it would have been obvious to one of ordinary skill in the art to use the composition of Schubert for the treatment of obesity.

Claims 1-27 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.